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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,946	10/02/2003	Jong Wook Hong	20174C-010310	7287

20350 7590 09/17/2009
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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
09/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/678,946	**Applicant(s)** HONG ET AL.	
	Examiner HEATHER G. CALAMITA	**Art Unit** 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _19 August 2009_.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _67,69-73 and 75-87_ is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) _67, 69-73 and 75-87_ is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 19, 2009, has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 67, 69-73 and 75-87 are currently pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 67, 69, 76 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (U.S. Patent No. 6,007,690, issued December 28, 1999) in view of Unger et al. (U.S. Patent No. 6,408,878, issued June 25, 2002).

Nelson et al. disclose a method of using an integrated microfluidic device, wherein said microfluidic device allows for the enrichment of a sample via an enrichment channel (column 2, lines 49-55). The artisans explicitly state that their integrated microfluidic device comprises a plurality of components (for various steps) in said single microfluidic device (column 4, lines 18-23).

Nelson et al. disclose that the enrichment channel of their microfluidic device serves to process an initial sample to enrich a particular fraction thereof (column 4, lines 47-48), allowing for the separation and selective retaining of target analytes (column 4, lines 50-52).

Nelson et al. disclose that a sample comprising heterogeneous biological elements are provided, and physically isolated a subset of said biological elements within a microfluidic device, wherein said elements are cells (column 24, lines 11-25).

Nelson et al. disclose that the isolated cells can be used in subsequent processes or analyses. (column 24, lines 12-13).

Nelson et al. also explicitly disclose that the purified/isolated cells are ready for direct use in reverse transcription coupled with polymerase chain reaction (RT-PCR).

Various reagents, including lysing reagents are injected through a sample injector port (column 22, lines 38-40).

Nelson et al. do not explicitly disclose a method of isolating a subpopulation of cells from a heterogeneous population, followed by a lysis of said isolated subpopulation, followed by an amplification the released nucleic acids.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to arrive at the claimed invention based on Nelson's teachings, for the following reasons.

Nelson et al., while not explicit in stating that a lysis step should follow subsequent to their explicitly disclose method of cell isolation, are implicit in stating that RT-PCR be conducted, which would necessarily require the disruption of the cells (i.e., lysis step), for the releasing of its nucleic acid contents.

Nelson et al. is explicit in evidencing the advantage provided for by the use of microfluidic device for the purpose of coupling many assays on a single device (column 2, lines 60-67).

In addition, Nelson et al. provides an explicit example of DNA purification which relies on the lysis of cells (column 23), for the PCR of released DNAs (column 23, line 45-47).

Lastly, Nelson et al. provides an explicit example of a device comprising a plurality of linked analyses units (Figure 16; column 17, lines 8-47).

Therefore, one of ordinary skill in the art, at the time the invention was made, would have been reasonable motivated to couple the cell isolation method and other nucleic acid analysis modules on a single device, thereby arriving at the invention as claimed.

Additionally, Nelson et al. do not teach allowing the elements to flow past a first valve and actuating the first valve and a second valve preventing the biological elements from exiting that segment of the flow channel. Nelson et al. do not teach the intersection of a first microfluidic flow channel and a second microfluidic flow channel. Nelson do not teach a rotary mixer. Applicants disclose in the instant specification at p. 33 lines 10 and 11 the rotary mixer may be a rotary pump.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Nelson et al. and Unger et al., thereby arriving at the claimed invention for the following reasons.

Nelson et al. is explicit in evidencing the necessity of retaining the sample in the flow chamber (see col. 5 lines 50-67 to col. 6 lines 1-10).

Unger et al. explicitly discloses the motivation to use valves and pumps in sample retention and control. Unger discloses

> Monolithic elastomeric valves and pumps also avoid many of the practical problems affecting flow systems based on electro-osmotic flow. Typically, electro-osmotic flow systems suffer from bubble formation around the electrodes and the flow is strongly dependent on the composition of the flow medium. Bubble formation seriously restricts the use of electro-osmotic flow in microfluidic devices, making it difficult to construct functioning integrated devices. The magnitude of flow and even its direction typically depends in a complex fashion on ionic strength and type, the presence of surfactants and the charge on the walls of the flow channel. Moreover, since electrolysis is taking place continuously, the eventual capacity of buffer to resist pH changes may also be reached. Furthermore, electro-osmotic flow always occurs in competition with electrophoresis. As different molecules may have different electrophoretic mobilities, unwanted electrophoretic separation may occur in the electro-osmotic flow. Finally, electro-osmotic flow can not easily be used to stop flow, halt diffusion, or to balance pressure differences.

> A further advantage of the present monolithic elastomeric valve and pump structures are that they can be actuated at very high speeds. For example, the present inventors have achieved a response time for a valve with aqueous solution therein on the order of one millisecond, such that the valve opens and closes at speeds approaching or exceeding 100 Hz. In particular, a non-exclusive list of ranges of cycling speeds for the opening and closing of the valve structure include between about 0.001 and 10000 ms, between about 0.01 and 1000 ms, between about 0.1 and 100 ms, and between about 1 and 10 ms.
> The cycling speeds depend upon the composition and structure of a valve used for a particular application and the method of actuation, and thus cycling speeds outside of the listed ranges would fall within the scope of the present invention.
>
> Further advantages of the present pumps and valves are that their small size makes them fast and their softness contributes to making them durable. Moreover, as they close linearly with differential applied pressure, this linear relationship allows fluid metering and valve closing in spite of high back pressures.

Based on such explicit motivation, one of ordinary skill in the art at the time the invention was made would have recognized the clear need to control and retain the sample in the flow chamber.

While Nelson et al. disclose a method of sample retention, one of ordinary skill in the art at the time the invention was made would have been motivated to employ the valves and pumps in the microfluidic system disclosed by Unger in the microfluidic system disclosed by Nelson et al. so as to benefit from the increased control and maneuverability of the sample in the device which is afforded by the valve and pump system disclosed by Unger et al.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

4. Claims 70-73, 75, 80, 83 84 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (U.S. Patent No. 6,007,690, issued December 28, 1999) and Unger et al. (U.S. Patent No. 6,408,878, issued June 25, 2002) in view of Burlage (US 2003/0099928, published May 29, 2003, priority September 16, 1999).

The teachings and suggestions of Nelson et al. and Unger et al. have already been discussed above.

Nelson et al. and Unger et al. do not teach or suggest that their microfluidic device should be employed in a method of obtaining characterizing phylogenetic, gene, and functional diversity exhibit by a specific environment.

Burlage discloses a method of separating particular cells from an environmental sample, wherein the method comprises:

a) providing an environmental sample comprising heterogeneous biological elements, wherein the elements are cells (section [0040]);

b) physically isolating an individual biological element or a subset of biological elements of the sample (sections [0010]; [0017]; [0035]; and [0065]);

c) lysing the isolated cells to liberate the nucleic acids present herein thereby releasing nucleic acid form the biological elements (section [0069]);

d) purification of the nucleic acids (section [0084]); and

e) amplification of the purified nucleic acid (sections [0069] and [0085]).

With regard to claim 71, the genetic diversity of a Pseudomonas is elucidated by sequence analysis (section [0088]).

With regard to claim 75, the artisans teaches that the isolated nucleic acid is cloned and cultured into a culturable microorganism to synthesize the gene product (section [0072]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Nelson et al. and Burlage, thereby arriving at the claimed invention for the following reasons.

The motivation to analyze unculturable microorganisms from an environmental sample comprising a heterogeneous population of microorganisms is explicitly disclosed by Burlage:

> "Unculturable microorganisms are those microorganisms that cannot be grown in pure cultures by known means. It has been hypothesized that majority of microorganisms are unculturable in any microbial environment, for reasons that are unclear. These unculturable microorganisms represent a vast, untapped resources of DNA and of potential products such as enzymes and other protein products. These microorganisms undoubtedly have undiscovered enzymes that would be useful for environmental, medical, or industrial applications. However, these potential products are currently unavailable because there is no way to obtain pure DNA from such microorganisms. Microorganisms are presently studied at the genetic level by cloning and sequencing their DNA. However, this requires the cultivation of a large number of cells with subsequent extraction of the DNA from the batch. The same approach obviously can not be used for unculturable microorganisms." (sections [0003] and [0004]).

Based on such explicit motivation, one of ordinary skill in the art at the time the invention was made would have recognized the clear need to separate and individually analyze unculturable microorganisms from a sample comprising a heterogeneous population of microorganisms such as an environmental sample.

While Burlage employs techniques such as FACS for cell sorting, followed by subsequent manual operation of DNA extraction, and amplification of the extracted nucleic acids, given the advantage of combining all of theses assays on a single microfluidic device (as disclosed by Nelson et al.), one of ordinary skill in the art at the time the invention was made would have been motivated to employ a microfluidic device which is well known and recognized in its ability to incorporate many biological assays into a single chip, so as to benefit from its ability to employ less sample/reagents, reduce the chances of contamination; and reduce the time required for the assay.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

5. Claims 77 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (U.S. Patent No. 6,007,690, issued December 28, 1999) view of Unger et al. (U.S. Patent No. 6,408,878, issued June 25, 2002).

The teachings of Nelson et al. have already been discussed above.

Nelson et al. do not explicitly disclose that a deflectable membrane be used so as to isolate their subset of biological elements, or that said deflectable membrane be activated by a control line.

Unger et al. disclose a microfluidic device with deflectable membrane (column 41, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Nelson et al. with the teachings of Unger et al., thereby arriving at the claimed invention for the following reasons.

While Nelson et al. are not explicit in stating that deflectable membrane should be used for moving and isolating a subset of biological elements, the artisans are clear in stating that any form of fluid control is adaptable:

> When convenient, e.g., for the introduction of wash and/or elution solvent into the enrichment channel, one or more additional fluid inlets may be provided to conduct such solvents into the enrichment channel from fluid reservoirs. To control bulk fluid flow through the enrichment channel, e.g., to prevent waste sample from flowing into the main electrophoretic flowpath, fluid controls means, e.g., valves, membranes, etc.., may be associated with each of the inlets and outlets (column 8, lines 33-40).

Therefore, one of ordinary skill in the art would have been motivated to adapt any of the well known prior art means to move and isolate samples within a microfluidic channel, yielding a predictable outcome.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

6. Claims 81, 82, 85, and 86 rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. (U.S. Patent No. 6,007,690, issued December 28, 1999) in view of Burlage (US 2003/0099928, published May 29, 2003, priority September 16, 1999) as applied to claims 70-73, 75, 80, and 84 above, and further in view of Unger et al. (U.S. Patent No. 6,408,878, issued June 25, 2002).

The teachings of Nelson et al. and Burlage have already been discussed above.

Neither Nelson et al. nor Burlage explicitly disclose that a deflectable membrane be used so as to isolate their subset of biological elements, or that said deflectable membrane be activated by a control line.

Unger et al. disclose a microfluidic device with deflectable membrane (column 41, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Nelson et al. and Burlage with the teachings of Unger et al., thereby arriving at the claimed invention for the following reasons.

While Nelson et al. are not explicit in stating that deflectable membrane should be used for moving and isolating a subset of biological elements, the artisans are clear in stating that any form of fluid control is adaptable:

> When convenient, e.g., for the introduction of wash and/or elution solvent into the enrichment channel, one or more additional fluid inlets may be provided to conduct such solvents into the enrichment channel from fluid reservoirs. To control bulk fluid flow through the enrichment channel, e.g., to prevent waste sample from flowing into the main electrophoretic flowpath, fluid controls means, e.g., valves, membranes, etc.., may be associated with each of the inlets and outlets (column 8, lines 33-40).

Therefore, one of ordinary skill in the art would have been motivated to adapt any of the well known prior art means to move and isolate samples within a microfluidic channel, allowing for a predictable outcome.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments

7. Applicants' arguments filed August 19, 2009, have been fully considered but they are not persuasive. Applicants argue the instant invention cells are not selected based on binding of an anti-ligand or affinity to a matrix but rather by partition in a microfluidic channel. This argument is not persuasive because Applicants use the language of comprising therefore additional elements can be present in the prior art. Nelson teach separation in a microfluidic channel using anti-ligand or affinity to a matrix. Nelson is not relied on for the teaching of valves but rather Unger et al. is relied on for and discloses the use of valves in microfluidic devices. Applicants argue Nelson do not teach the biological elements may include combinations of cells that do not share a particular characteristic ligand recognized by a binding agent. This argument is not persuasive as Applicants are arguing limitations not currently recited in the instant claim.

Applicants argue the office incorrectly equates "sample retention" with "flow systems" and that the correct analogy is between "sample retention" and "electrophoretic flowpath." This argument is not persuasive as Applicants simply assert the analogy is not correct. As outlined in the rejection above Unger provides motivation to modify Nelson. Applicants argue affinity based selection of the cells or molecules in solution is not equal to physical segregation or partition of the solution itself and states that the current invention may result in isolation of combinations of biological elements that do not share a particular property and may result in separation of identical biological elements away from each other. This argument is not persuasive because there is currently no limitation in the claims requiring separation of identical biological elements away from each other. Additionally, the solution of Nelson is physically separated in that some of the molecules in solution are separated (because the molecules are retained the solution is physically separated) from other molecules and fluids in the solution.

Finally with respect to claim 87 and a cross-flow injector, Nelson teaches the lysing chemical as outlined in the rejection above and Unger is relied on for the "cross-flow injector." Unger teaches using micropumps. A pump is the same thing as an injector. With respect to claim 87, Unger discloses mixing of reagents in a rotary fashion.

Summary

8. No claims were allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic

Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Heather G. Calamita/
Examiner, Art Unit 1637